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(54) Title: SELF-EMULSIFYING FENOFIBRATE FORMULATIONS

(57) Abstract

Pharmaceutical oral dosage forms for fenofibrate are described in which the active drug is formulated as storage stable self-emulsifying preconcentrate composed of an oil phase including triglycerides, fish oils, free fatty acids and esters, vegetable oils, a non-ionic surfactant and a hydrophilic component such as hydroxy alkanes, polyethylene glycols and the like. Increase fenofibrate results.

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SELF-EMULSIFYING FENOFIBRATE FORMULATIONS

BACKGROUND AND SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical dosage form of fenofibrate with a potential for enhanced bioavailability.

The term "composition" as used herein shall mean any composition containing a therapeutic agent along with inactive ingredients that are themselves pharmaceutically acceptable in the quantities administered.

The term "carrier medium" as used herein is to be understood as defining the material in which the drug (i.e. fenofibrate) is dissolved. The carrier medium may be a single or a combination or mixture of ingredients included as solvents, surfactants, diluents or for other purposes.

Fenofibrate or 2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-propanoic acid 1-methylethyl ester is a potent lipid modulator agent; it offers unique and significant clinical advantages over existing products in the fibrates class of drugs. Fenofibrate produces substantial reductions in plasma triglyceride levels in hypertriglyceridemic patients and in plasma cholesterol and LDL-cholesterol in hyperhypercholesterolemic and mixed dyslipidemic patients.

Fenofibrate is a prodrug which immediately after absorption is hydrolyzed by tissue and plasma esterases to its active major metabolite, fenofibric acid. Fenofibric acid is responsible for the pharmacological activity and its plasma half-life is about 20 hours. Fenofibrate is practically

insoluble in water, it is poorly and variably absorbed and has to be taken with food.

Fenofibrate was first available in a pharmaceutical dosage form (Lipanthyl® also marketed under the trademarks Lipidil® and Lipantil®) consisting of a hard gelatin capsule containing fenofibrate, lactose, pregelatinized starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is effectively absorbed and found in the blood as fenofibric acid (Weil et al., The metabolism and disposition of 14C-fenofibrate in human volunteers, Drug. Metabol. Dispos. Biol. Fate. Chem., 18 (1990) 115-120).

Historically, in order to improve the intestinal absorption, another pharmaceutical dosage form was introduced (Lipidil Micro®, also marketed under the trademarks Lipanthyl® and Tricos®). European Patent Application 330,532 and U.S. patent 4,895,726 disclose a fenofibrate composition in which the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl sulfate is described as the wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipients such as lactose, starch, cross-linked polyvinyl pyrrolidone and magnesium stearate. A study comparing this formulation (Lipidil Micro®) to the conventional form (Lipidil®) had showed statistically significant increase in bioavailability with the former.

However, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, has several drawbacks such as irritation of mucosal membranes of the gastrointestinal

tract. In addition, micronization is a time consuming and costly operation and the filling of hard gelatin capsules with a micronized powder is a difficult operation when taking into account weight variation homogeneity.

European Patent Application 724,877 describes fenofibrate powder co-micronized with a wetting agent in association with a vitamin E component (tocopherol and/or its organic acid ester) for treating or preventing disorders associated with lipoprotein oxidation.

U.S. patent 4,800,079 relates to a medicinal composition in the form of granules with controlled release of fenofibrate. Each granule includes an inert core, a layer based on fenofibrate and a protective layer. Fenofibrate is present in the form of crystalline microparticles of dimensions not greater than 30 μm.

U.S. patent 4,961,890 relates to a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles (< 30 μm in diameter) within a multilayer layer inert matrix.

U.S. patent 5,545,628 relates to a pharmaceutical composition for treating hyperlipidemia or hypercholesterolemia or both in a mammal, by providing an effective amount of each of fenofibrate and an excipient including one or more polyglycolyzed glycerides (generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters if polyethylene glycols). The polyglycolyzed glycerides may be obtained by partial transesterification of triglycerides

with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids.

European Patent Application 757,911 relates to a fenofibrate pharmaceutical dosage form in which fenofibrate is in solution in diethylene glycol monoethyl ether (EMDG) which is a non ionic surfactant.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a graph showing the data obtained in Example 12, and

Figure 2 is a graph showing the results obtained in Example 13.

SUMMARY OF THE INVENTION

In accordance with the present invention it has now surprisingly been found that particularly stable fenofibrate formulations that self emulsify in aqueous medium giving an average particle size in a range of about 10 nm to about 10 microns and that have improved bioavailability characteristics, are obtainable. Also described are self-emulsifying preconcentrates that disperse, without the input of high energy (i.e., other than mixing energy to cause dispersion), to form droplets of average size of up to about 10 microns.

Accordingly, this invention provides a pharmaceutical composition in the form of a self-emulsifying preconcentrate comprising fenofibrate as the active ingredient solubilized in a carrier medium comprising at least one hydrophobic component, at least one hydrophilic component and at least one surfactant.

The self-emulsifying systems and their corresponding preconcentrates described in this invention consist of a hydrophobic component, an ingredient selected from triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters (such as fatty acid esters of hydroxyalkanes or of dihydroxyalkanes) and derivatives thereof, individually or in combination. Preferably the surfactant is a non-ionic surfactant or a mixture of non-ionic surfactants. The invention is also characterized as optionally including a hydrophilic component, for instance a hydroxyalkane such as ethanol and/or a dihydroxyalkane such as 1,2-propylene glycol and/or a polyethylene glycol having an average molecular weight of less than or equal to 1000.

DETAILED DESCRIPTION OF THE INVENTION

A self-emulsifying preconcentrate comprising fenofibrate of the present invention must contain a hydrophobic component, a surfactant and optionally a hydrophilic component.

The surfactant and hydrophilic component are needed for the composition to form in aqueous medium a self-emulsifying system having an average particle size of between about 10 nm and about 10 microns, and preferably at most 5 microns. They may also help enhance the solubility and stability of fenofibrate in the formulation.

The hydrophobic component is needed because if it is not incorporated in appropriate amounts in the formulation, precipitation of

fenofibrate will be observed upon mixing of the composition with an aqueous medium and/or on storage. Similar observations may be made for the hydrophilic and surfactant components.

Based on the above, appropriate combinations or mixtures of a hydrophobic component, a surfactant and a hydrophilic component (when used) with fenofibrate are necessary to obtain a stable microemulsion preconcentrate that would yield upon mixing with an aqueous medium a stable dispersion with an average particle size of between about 10 nm and about 10 microns.

Preferred as hydrophobic components are triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters and derivatives thereof, individually or in combination. Examples of hydrophobic components include but are not limited to propylene glycol dicaprylate/caprate, caprilic/capric triglyceride, caprylic/capric/linoleic triglyceride, e.g., synthetic medium chain triglycerides having C_{8-12} fatty acid chains or other derivatized (synthetic) triglycerides of the type known and commercially available under Miglyol 810, 812, 818, 829 and 840, linoleic acid, linoleic acid ethyl ester, fish oils as free fatty acids, their esterification and their transesterification products, e.g., of the type known and commercially available under EPAX 6000 FA, EPAX 4510 TG, individually or in combination. Additional examples include vegetable oils and C_{12-18} fatty acid mono-, di- and triglycerides prepared by individual admixing or as transesterification products of vegetable oils (such as soybean oil, almond oil, sunflower oil, olive oil or corn oil) with glycerol.

Preferred as hydrophilic components are 1,2-propylene glycol, ethanol and polyethylene glycol having an average molecular weight of less than or equal to 1000, individually or in combination.

More preferred as hydrophilic components are 1,2-propylene glycol and ethanol, individually or in combination.

Especially preferred as hydrophilic components is a combination or mixture of 1,2-propylene glycol and ethanol.

Compositions of the current invention will include, in addition to fenofibrate, the hydrophobic components and the optional hydrophilic components, and at least one surfactant. Examples of suitable surfactants are:

1. Polyoxyethylene-sorbitan-fatty acid esters; e.g., mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g., products of the type known as polysorbates and commercially available under the trade name "Tween".
2. Polyoxyethylene fatty acid esters, e.g., polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj.
3. Polyoxyethylene castor oil derivatives, e.g., products of the type known and commercially available as Cremophors. Particularly suitable are polyoxyl 35 castor oil (Cremophor EL) and polyoxyl 40 hydrogenated castor oil (Cremophor RH40).
4. alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS).

5. PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylatc/capratc (commcrcially known as Labrasol), PEG-4 glyccryl caprylate/caprate (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 44/14),), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS).
6. Propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate; also diethylene glycol monoethyl ether, commercially known as transcutol.
7. Sorbitan fatty acid esters, such as the type known and commercially available under the trade name Span (e.g., Span 20).
8. Polyoxyethylene-polyoxypropylene co-polymers, e.g., products of the type known and commercially available as Pluronic or Poloxamer.
9. Glycerol triacetate.
10. Monoglycerides and acetylated monoglycerides, e.g., glycerol monooleate, glycerol monostearate and mono-and di- acetylated monoglycerides.

Suitable surfactants are not limited to those mentioned above, but may include any compound that would enhance the galenic properties of the preconcentrate.

Compositions in accordance with the present invention may include other ingredients in addition to the drug, one or more hydrophobic components, one or more hydrophilic components and one or more surfactants. For example, the composition may include, in addition to the forgoing, one or more ingredients, additives or diluents such as

pharmaceutically acceptable polymeric or inorganic materials, anti-oxidants, preserving agents, flavoring or sweetening agents and so forth.

Compositions in accordance with the present invention may be liquid or solid at ambient temperature. They may be filled in soft or hard gelatin capsules in the form of liquid composition, molten composition, or granules or powder (if composition is solid at ambient temperature and was cooled and processed before filling). Coating may be also applied to capsules or tablets. The preconcentrate may be also diluted with water to obtain stable emulsion that may be employed as drinking formulations, for example.

The relative proportion of fenofibrate and the other ingredients in the composition of the current invention, will vary depending whether it is delivered as a self-emulsifying preconcentrate or after dilution with water, depending on the particular ingredients and the desired physical properties of the formulation. Especially desired concentration limits in the self-emulsifying preconcentrate:

1. Oil phase: from 10 to 85% w/w of the preconcentrate. The oil phase may consist of triglycerides, diglycerides, monoglycerides, free fatty acids, propylene glycol mono or diesters and free fatty acids, esters and derivatives thereof, individually or in combination.
2. Cumulative amounts of surfactants: from 10 to 80% w/w of the preconcentrate.
3. Cumulative amounts of hydrophilic components, such as 1,2-propylene glycol and/or ethanol and/or a polyethylene glycol having an average molecular weight of less than or equal to 1000 : from 0%

to 40% w/w of the preconcentrate. The total of all ingredients will be 100%.

The oral dosage range for a typical preconcentrate according to the invention per 100 mg fenofibrate is estimated to vary between 700-3000 mg. For lower amounts of drug, the total quantity of ingredients may be proportionally reduced.

The following are illustrative but non limiting examples of compositions in accordance with the present invention.

Examples

In the following examples, the ingredients were weighed out into appropriate containers in the amounts described below. In all examples described below, a clear liquid was obtained upon appropriate mixing and heating.

The formulations represented in the following examples were prepared by mixing the oil components with the drug powder followed by the addition of surfactants and cosurfactants as indicated. The composition may be prepared at room temperature or heated to 40-50°C to accelerate the solubilization process. Several mixing techniques can be used ranging from mechanical stirring and agitation to sonication.

All compositions shown below give liquid or semi-solid preconcentrates at room temperature.

In vitro testing of the preconcentrates was carried out by diluting the preconcentrate in 50-100 fold water or simulated gastric fluid with gentle mixing or shaking. The aqueous medium temperature varied between 20 and 37°C. Particle size analysis was then carried out using a Nicomp 370. Data reported in the following examples correspond to volume weighted distributions.

Example 1: Composition comprising 100 mg fenofibrate

Mean particle size : 50 nm

Excipients	Quantity (mg)
Miglyol 810	250
Linoleic acid	130
Tween 80	200
Myrj 52	170
VitE-TPGS	108
Ethanol	126
1,2-propylene glycol	124

Example 2: Composition comprising 100 mg fenofibrate

Mean particle size : 20 nm

Excipients	Quantity (mg)
Miglyol 810	250
Linolcic acid	130
Tween 80	375
VitE-TPGS	76
Ethanol	126
1,2-propylene glycol	125

Example 3: Composition comprising 100 mg fenofibrate

Mean particle size : 30 nm

Excipients	Quantity (mg)
Linoleic acid ethyl ester	350
Tween 80	350
VitE-TPGS	90
Span 20	100
Ethanol	150
1,2-propylene glycol	75

Example 4: Composition comprising 100 mg fenofibrate

Mean particle size : 30 nm

Excipients	Quantity (mg)
Miglyol 840	360
Tween 40	235
Tween 80	235
VitE-TPGS	75
Span 20	150
Ethanol	150
1,2-propylene glycol	75

Example 5: Composition comprising 100 mg fenofibrate

Mean particle size : 90 nm

Excipients	Quantity (mg)
Miglyol 840	360
Tween 40	270
Tween 80	114
VitE-TPGS	75
Cremophor EL	160
Ethanol	140
1,2-propylene glycol	75

Example 6: Composition comprising 100 mg fenofibrate

Mean particle size: 10 nm

Excipients	Quantity (mg)
Miglyol 810	280
Linoleic acid	130
Tween 80	520
Ethanol	120
Labrasol	20

Example 7: Composition comprising 100 mg fenofibrate

Mean particle size: 25 nm

Excipients	Quantity (mg)
Miglyol 810	280
Linoleic acid	130
Tween 80	484
Ethanol	40
Labrasol	54
1,2-propylene glycol	20

Example 8: Composition comprising 100 mg fenofibrate

Mean particle size: 40 nm

Excipients	Quantity (mg)
Miglyol 840	435
Tween 80	473
Ethanol	100
Span 80	127

Example 9: Composition comprising 100 mg fenofibrate

Mean particle size: 45 nm

Excipients	Quantity (mg)
Miglyol 840	360
Linoleic acid	75
Tween 80	464
Ethanol	120

Example 10: Composition comprising 100 mg fenofibrate
Mean particle size 40 nm

Excipients	Quantity (mg)
Miglyol 840	435
Span 20	135
Tween 80	470
Ethanol	100

Example 11: Composition comprising 100 mg fenofibrate
Mean particle size 40 nm

Excipients	Quantity (mg)
Miglyol 840	429
Inwitor 742	233
Cremophor EL	291

Example 12: Effect of Dilution on Particle Size of Self-Emusifying (SE-) Fenofibrate Formulation

The fenofibrate preconcentrate prepared in Example 11 was diluted in various ratios either with deionized water (DW) or with simulated gastric fluid (SGF) with gentle mixing at 35-37°C. Volume weighted particle size analysis of the diluted emulsion was then performed using Nicomp 370 particle size analyzer. As can be seen from the data presented in the following table, the formation of microemulsion is independent of the dilution factor.

Dilution factor	Clarity		Average particle size (nm)	
	DW	SGF	DW	SGF
1	Clear	Clear	38	41
5	Translucent	Translucent	47	58
10	Translucent	Translucent	46	54
20	Translucent	Translucent	40	44
50	Translucent	Translucent	39	38

Example 13: Increase in Oral Bioavailability of SE-Fenofibrate in Beagle Dogs

Oral administration of the SE-fenofibrate of Example 10 was compared with the commercially available Lipanthyl® 67M formulation in two male and two female beagle dogs per group. Each group was administered either the commercial formulation or SE-fenofibrate of Example 10 each containing 67 mg of the drug per dose. Blood samples after each administration were collected at 0.5, 1, 2, 3, 4, 6, 24, and 48 hours. Fenofibrate concentration of each blood plasma sample was determined by high pressure liquid chromatography by monitoring for the level of the metabolite, finofibric acid. The data are presented in the attached graph, Figure 1, in which solid squares represent the self-emulsifying fenofibrate preconcentrate of the present invention and the solid triangles represent the commercial product. At equivalent dose, the bioavailability of the drug was about 30% higher in case of the SE-fenofibrate of Example 10 than the commercial formulation. In a similar study in human subjects (n=8 per group), the bioavailability of SE-fenofibrate of Example 11 was about 57% higher than that of the

commercial formulation.

Example 14: Effect of Food on Oral Bioavailability of SE-Fenofibrate in Human Subjects

The SE-fenofibrate composition used in Example 11 was tested in human volunteers. The study consisted of oral administration of the fenofibrate formulation to eight human volunteers per group in a cross-over design in fed or fasted state. Each group was administered fenofibrate containing 67 mg of the drug. Blood samples were taken before and after each administration at various time points over 120 hours. Drug concentration in blood samples was determined by high pressure liquid chromatography by monitoring for the level of the metabolite, fenofibric acid. The data are presented in Fig. 2. At equivalent dose, the ratio of bioavailability in fasted and fed state was 0.99 (90% confidence interval: 0.91-1.06) indicating that the bioavailability of SE-fenofibrate formulation is independent of food intake.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising fenofibrate as active ingredient dissolved in a carrier system comprising a hydrophobic component, a hydrophilic component and at least one surfactant, wherein the hydrophobic component is selected from triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters and derivatives thereof, individually or in combination and wherein the hydrophilic component is a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of less than or equal to 1000 or mixtures thereof.

2. A pharmaceutical composition consisting essentially of fenofibrate dissolved in a carrier system composed of a surfactant, an oil phase comprising a triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester or mixtures thereof and hydrophilic phase comprising a hydroxyalkane, a dihydroxyalkane, polyethylene glycol having a molecular weight of at most 1000.

3. The composition of claim 1 or claim 2 wherein the hydrophobic component is a fatty acid ester of a hydroxyalkane, a fatty acid ester of a dihydroxyalkane, a fatty acid mono-, di- or triglyceride or a transesterification product of a vegetable oil with a glycerol.

4. The composition of claim 1 or claim 2 wherein the hydrophilic component is 1,2-propylene glycol, ethanol, a polyethylene glycol or mixtures thereof.

5. The composition of claim 1 or claim 2 wherein at least one surfactant is non-ionic.

6. A storage-stable self-emulsifying preconcentrate of fenofibrate composed of:
10 to 85% w/w of an oil phase of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil and mixtures thereof;
10 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and
0 to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, dihydroxy alkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof
wherein said preconcentrate, when mixed with an aqueous medium gives an average particle size of at most 10 microns.

7. The self-emulsifying preconcentrate of claim 6 containing from 15 to 75% w/w oil phase.

8. The self-emulsifying preconcentrate of claim 6 containing from 15 to 75% w/w surfactant.

9. The self-emulsifying preconcentrate of claim 6 containing up to 30% w/w hydrophilic component.

10. A storage-stable, self-emulsifying, clear, liquid preconcentrate of fenofibrate consisting essentially of:

10 to 85% w/w of an oil phase of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil and mixtures thereof;

10 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and

up to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, a dihydroxy alkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof

wherein said preconcentrate, when mixed with an aqueous medium gives an average particle size of at most 5 microns, or which upon oral administration forms *in situ* a microemulsion in the gastrointestinal tract.

11. The self-emulsifying preconcentrate of claim 6 or 10 wherein a hydrophilic component is present and is selected from 1,2-propylene glycol, ethanol, polyethylene glycol having an average molecular weight of less than or equal to 1000 and combinations thereof.

12. The self-emulsifying preconcentrate of claim 6 or 10 wherein a hydrophilic component is present and is a mixture of 1,2-propylene glycol and ethanol.

13. The self-emulsifying preconcentrate of claim 6 or 10 wherein a hydrophilic component is present and at least one non-ionic surfactant is present.

14. The self-emulsifying preconcentrate of claim 6 or 10 wherein a hydrophilic component is present and the hydrophobic component is a fatty acid ester of a hydroxyalkane, a fatty acid ester of a dihydroxyalkane, a fatty-acid mono-, di-or tri-glyceride or a transesterification product of a vegetable oil with a glycol.

15. A method of orally administering fenofibrate to a subject in need of same comprising an orally active, storage-stable, self-emulsifying preconcentrate of solubilized fenofibrate composed of:

10 to 85% w/w of an oil phase of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil and mixtures thereof;

10 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and

up to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, a dihydroxy alkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof

wherein said preconcentrate, when mixed with an aqueous medium gives an average particle size of at most 5 microns.

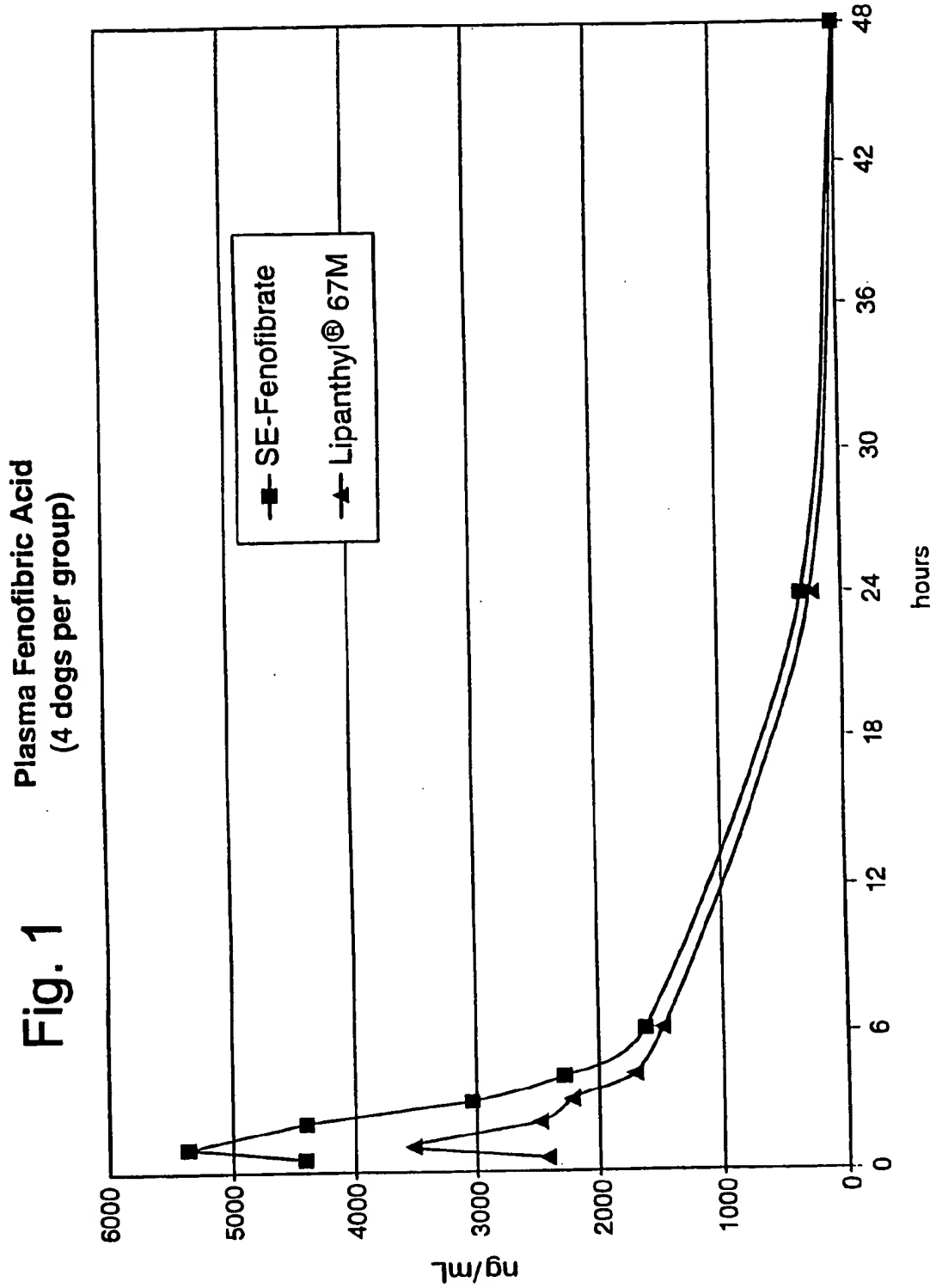
16. A method of orally administering a self-emulsifying preconcentrate comprising fenofibrate solubilized in a stable, self-emulsifying system which self-disperses in water, simulated intestinal, or

simulated gastric fluid to yield a homogeneous phase with a droplet size of below 5 microns.

17. A method of enhancing the oral bioavailability of fenofibrate comprising solubilizing fenofibrate in a stable, self-emulsifying system which upon oral administration self-disperses in aqueous medium to yield a homogeneous phase with a droplet size of below 5 microns.

18. A method of eliminating or reducing the need for concomitant food intake to obtain clinically effective blood levels of fenofibrate comprising administering to a subject in need of same a self-emulsifying fenofibrate formulation.

Fig. 1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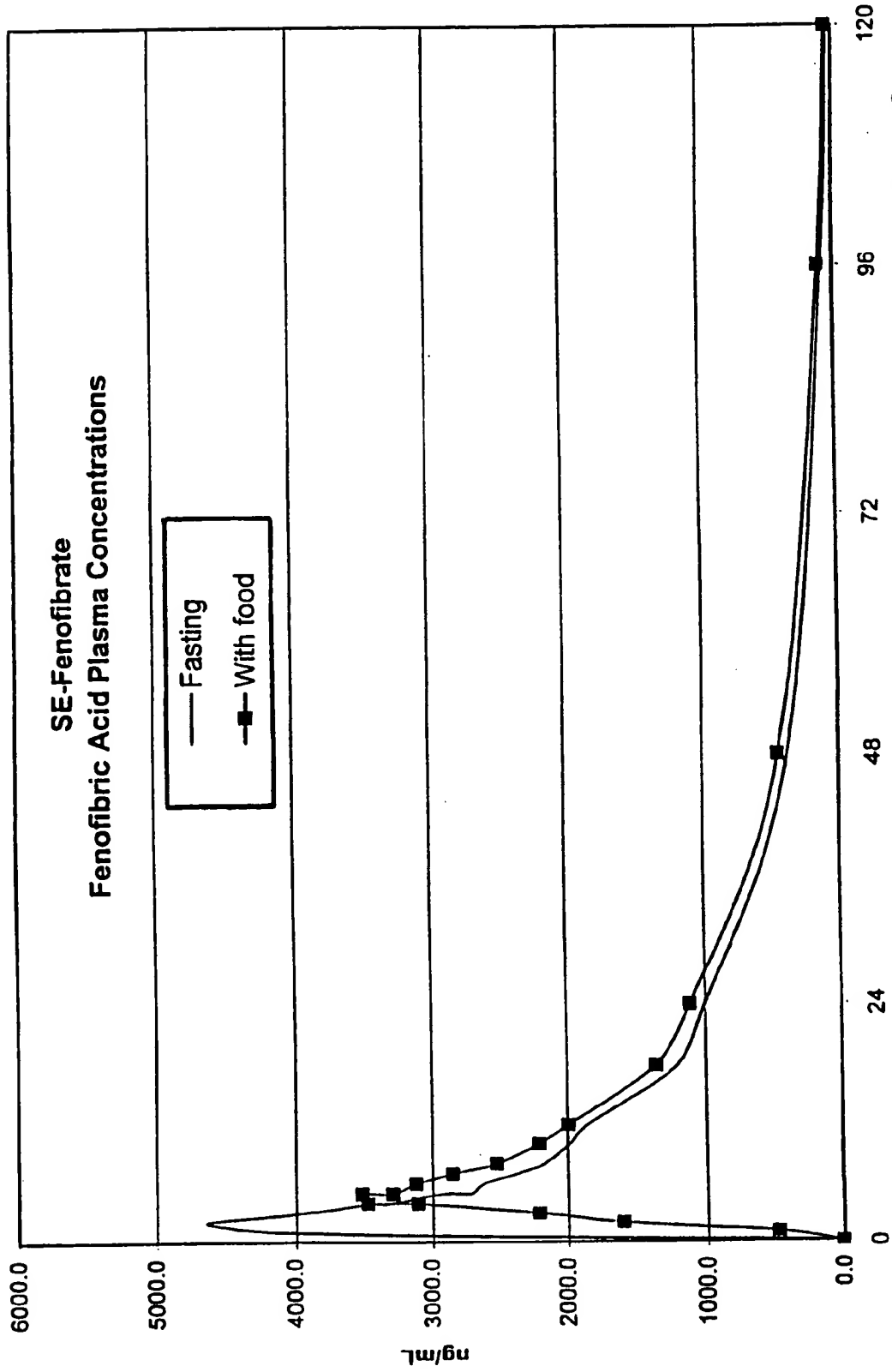
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Fasting
With food
ng/mL
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5000.0
4000.0
3000.0
2000.0
1000.0
0.0
0
24
48
72
96
120
hours

Fig. 2

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 98/26075

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K31/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 617 047 A (SANOFI) 30 December 1988 see claims 8-11 see example 1 ---	1-18
A	DE 34 21 468 A (RENTSCHLER) 19 December 1985 see claims see page 4, line 16 - line 20 ---	1-18
A	WO 94 20072 A (PHARMACIA) 15 September 1994 see claims ---	1-18
A	EP 0 757 911 A (CL PHARMA) 12 February 1997 cited in the application see the whole document --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1999	15/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/US 98/26075

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 724 877 A (FOURNIER) 7 August 1996 cited in the application see the whole document	1-18
A	WO 96 21439 A (GALEPHAR) 18 July 1996 cited in the application see the whole document	1-18
A	EP 0 330 532 A (FOURNIER) 30 August 1989 cited in the application see the whole document	1-18

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 26075

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 15-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 98/26075

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